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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte EDWIN WANG, JIE LI, YINGHAI DENG,
ANNE E. G. LENFERINK, MAUREEN D. O'CONNOR-McCOURT,
and ENRICO PURISIMA

Appeal 2016-002484
Application 13/263,426
Technology Center 1600

Before DEMETRA J. MILLS, JEFFREY N. FREDMAN, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a process for determining predictive gene expression signal sets. The Examiner rejected the claims as being directed to non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as The National Research Council of Canada (*see* App. Br. 2).

Statement of the Case

Background

"There is not currently a satisfactory approach to determine which patients with cancer would benefit from extra therapy (such as chemotherapy) after surgery. The identification of genes and proteins specific to cancer cells that can be used for prognostic purposes would be helpful in this regard" (Spec. 1:13–17).

The Claims

Claims 6–17 are on appeal. Claim 6 is representative and reads as follows:

> 6. A process for determining predictive gene expression signal sets comprising the following steps:
>
> 1) obtaining gene expression signal information and patient clinical information for a characteristic of interest for a known tumour population for a cancer of interest;
>
> 2) correlating the gene expression signals with clinical patient information regarding the characteristic of interest to identify which genes have predictive power for clinical outcome;
>
> 3) creating at least 30 random training datasets from the identified gene expression signals;
>
> 4) comparing identified gene expression signals of step 1 to a list of known genes active in cancer;
>
> 5) selecting identified gene expression signals which correspond to those on the list of known cancer genes;
>
> 6) grouping the selected identified gene expression signals according to their role in biological processes;
>
> 7) generating random gene expression signal sets of at least 25 genes from a selected gene expression signals group of step 6;

8) correlating the random gene expression signal sets to the random training datasets obtained in step 3;

9) obtaining a P value for a survival screening from the correlation for each gene expression signal set of step 7;

10) if the P value for a gene expression signal set is less than 0.05 for more than 90% of the random training datasets, keeping the gene expression signal set;

11) ranking the random gene expression signal sets kept in step 10 based on frequency of gene appearances in the set;

12) selecting the top at least 26 genes as potential candidate markers;

13) repeating steps 7 to 12 and producing another, independent, rank set of at least 26 genes;

14) comparing the top genes from step 12 and step 13;

15) if more than 25 of the genes are the same, the top genes are kept as marker sets;

16) twice repeating steps 7 to 15 to obtain three different marker sets;

17) outputting said three different marker sets.

The Issue

The Examiner rejected claims 6–17 under 35 U.S.C. § 101 as being directed to non-statutory subject matter (Final Act. 4–7).

The Examiner finds that claim 6 is "directed to a method for determining predictive gene expression signal sets comprising obtaining gene expression signals, and correlating the gene expression signals with clinical information to identify which genes are predictive, which is a natural phenomenon" (Final Act. 4). The Examiner further finds

> the steps append well-understood, routine and conventional activities previously known in the industry (obtaining gene expression) which is specified at a high level of generality. The

> steps do not impose meaningful limits on the claim scope and are only insignificant extrasolution activity because obtaining gene expression signal information and patient clinical information and correlating the gene expression signal with the clinical information are steps that are necessary for all practical applications of the natural principle and everyone practicing the natural principle would be required to perform these steps. Furthermore, the additional steps (creating, comparing, selecting, generating, correlating, ...) are mental steps, and complete absence of a machine-or-transformation in a claim signals the likelihood that the claim is directed to a natural principle and has not been instantiated.

(Final Act. 6). The Examiner concludes "the steps do not add 'significantly more' than the judicial exception, and therefore, the claims are not directed to patent subject eligible matter" (Final Act. 6).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that claim 6 is directed to non-statutory subject matter?

Findings of Fact

1. The Specification teaches "it will be desirable to study tumour tissue for a patient by extracting gene expression signals (e.g. mRNA, protein) and assaying the presence (and in some cases level) of gene expression signals of interest using a reporter specific for the gene expression signal of interest" (Spec. 12:11–14).

2. The Specification teaches prior art screening techniques were used where "surface and secreted proteins were identified from the microarray data of JM01 cell line (mouse breast cancer cell line, in-house cell line and data), to screen a public breast cancer dataset (295 samples, Chang et al., PNAS 102:3738, 2005)" (Spec. 14:3–6).

3. The Specification teaches: "Detailed information for making microarray gene chip, scanning and normalization of array data can be found at Agilent company website: http://www.chem.agilent.com/enUS/products/instruments/dnamicroarrays/pages/default.aspx.and [sic] in the publicly available literature" (Spec. 23:21–25).

4. The Specification teaches: "All message RNA sequences for each gene in Table 1 are extracted from ***National Center for Biotechnology Information (NCBI),*** a public database" (Spec. 31:4–6) (emphasis original).

5. The Specification teaches that prior art data was used as training sets, specifically: "In Example 1, two training datasets, defined as Dataset 1 (78 samples, van't Veer et al., Nature, 2002), and Dataset 2 (286 samples, Wang et al., Lancet, 365:671, 2005), were used" (Spec. 14:19–21).

6. The Specification teaches prior art software and information was used to obtain signal lists, specifically:

> Using the St-ER+ gene expression signal list, Gene Ontology (GO) analysis (using GO annotation software, David, http://david.abcc.ncifcrf.qov/) is performed, only the genes which belong to GO terms that are known to be associated with cancer, such as cell cycle, cell death and so on are used for further marker screening.

(Spec. 15:7–11).

7. The Specification teaches application of known statistical techniques, specifically that "statistical significance of the correlation between the expression values of each random-gene-set (30 genes) and patient survival status ('good' or 'bad') is examined, for example by performed Kaplan-Meier analysis by implementing the Cox-Mantel log-rank test" (Spec. 15:21–24).

8. The Specification teaches the "prior art discloses five such gene expression signal sets and these have been developed as biomarkers for breast cancer samples" (Spec. 2:22–24).

Principles of Law

> [W]e set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "inventive concept" -- *i.e.*, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014).

Analysis

We agree with and adopt the Examiner's findings of fact and reasoning regarding the conclusion that claim 6 is unpatentable as being directed to non-statutory subject matter consistent with binding precedent (Final Act. 4–7; FF 1–8). We address Appellants' arguments below.

Appellants contend

> the subject matter of the rejected claims is not "natural" in the sense that the data set and the marker set will never be identified or "naturally occurring" in a single individual. The presently claimed process is not a test to identify a naturally occurring gene which directly correlates with a cancer prognosis.

(App. Br. 7).

We do not find this argument persuasive because the underlying information in claim 6 is "gene expression signal information" that is associated with "a characteristic of interest for a known tumour population" and is then subjected to further analytical processes as recited in claim 6. The signals from the microarray represent natural levels of gene expression in naturally occurring tumors in patients (FF 1, 8). Applying the first step of the two step test in *Mayo* and *Alice*, we agree with the Examiner that the gene expression signal information is directed to a patent-ineligible concept, specifically laws of nature regarding expression levels of genes in tumors. This is factually similar to *Mayo* itself, where the underlying levels of 6-thioguanine were "naturally occurring," like the gene expression signal information in the instant case, and not medical applications that were "not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 80 (2012).

> Appellants contend
>
> the rejected claims calls for 17 steps to be carried out in a particular order, with separate numeric requirements for many of the steps (for example, step 3: "*at least 30* random training datasets;" step 7: "generating random gene expression signal sets of *at least* 25 genes.; step 12: selecting "the top *at least 26 genes* as potential candidate markers."). While each of these steps, in isolation, represents practice of a known scientific technique, when taken together as a whole, they constitute *significantly more* than a judicial exception.

(App. Br. 9).

We do not find Appellants' argument persuasive. "*Mayo* demanded that, when a claim involves . . . a law of nature . . . eligibility under section 101 requires that the claim involve 'enough' else—applying the idea in the realm of tangible . . . physical actions (for process claims)—that is beyond 'well-understood, routine, conventional activity.'" *SmartGene, Inc. v. Advanced Biological Laboratories, SA*, 555 F. App'x. 950, 955 (Fed. Cir. 2014).

The claim here does not do so. Under the second step of the two-step test, we find that claim 6 does not add "significantly more" to the natural law of gene expression levels in tumors. Each step of claim 6 is based on routine, prior art, conventional activity as acknowledged by Appellants' own Specification. Thus, step (1) of obtaining gene expression signal information uses known prior art microarray technologies (FF 3). The correlating steps (2) and (8), obtaining a P value steps (9) and (10) and ranking step (11) rely on known statistical techniques (FF 7). The creating training data set step (3) uses prior art datasets (FF 5). The comparison of signals step (4) and selecting and grouping those associated with known cancer genes steps (5) and (6) rely on prior art data for the cancer genes (FF 6, 8) and known prior art normalization approaches (FF 3). Repeating known steps does not add "significantly more."

Thus, Appellants do not identify any step that is something other than applying known methods of gathering and processing known types of information. We note that "[c]laims directed to the 'process of gathering and analyzing information of a specified content, then displaying the results,' without 'any particular assertedly inventive technology for performing those functions,' were held ineligible in *Electric Power Grp.*,

LLC v. Alstom S.A., 830 F.3d 1350, 1354 (Fed. Cir. 2016)." *Trading Techs. Int'l, Inc. v. CQG, INC.*, 2017 WL 192716 *3 (Fed. Cir. 2017). We find claim 6 analogous to the claims held patent ineligible in *Electric Power*.

"Merely requiring the selection and manipulation of information . . . by itself does not transform the otherwise-abstract processes of information collection and analysis." *Electric Power*, 830 F.3d at 1355. Appellants do not identify any technological advance to the process of analyzing the data, but simply select particular known data manipulations. Thus, we agree with the Examiner that the claim limitations, analyzed alone and in combination, fail to add "something more" to "transform" the claimed abstract idea of weighting informative sequence regions to obtain optimal reference sequences for use in organism classification into "a patent-eligible application." *See Alice*, 134 S. Ct. at 2354, 2357.

Appellants contend that claim 6 "recites a process that includes *17 steps*. These steps place meaningful limits on the scope of the rejected claims, such that the claims do not foreclose all applications of the natural principle that gene expression is correlated with certain clinically important characteristics" (App. Br. 9; *cf.* App. Br. 11).

We find this argument unpersuasive because "[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379 (Fed. Cir. 2015). Importantly, the preemption concern is addressed by the two-part test considered above. *See id.* After all, every patent "forecloses . . . future invention" to some extent, *Mayo*, 566 U.S. at 86, and, conversely, every claim limitation beyond those that recite the abstract idea limits the scope of the preemption.

Appellants "submit that the Examiner's interpretation is not the broadest *reasonable* construction of the claim . . . Applicants respectfully submit that the claims are not reasonably read to encompass 'mere inspection' of the data by an individual" (App. Br. 10).

We find this argument unpersuasive because the issue is not whether the claims may be performed by an individual, but rather whether the claims are drawn to a patent ineligible natural concept and whether the claims add significantly more to that concept. For the reasons given above, we find that consistent with binding precedent, claim 6 does not satisfy this two-part test and is drawn to non-statutory subject matter.

We do note that the Examiner finds: "It was well known in the industry to compare expression signal and patient data to create training sets and generating gene expression signals to identify predictive gene expression signal sets" (Ans. 9) and this finding is supported by the Specification itself which recognizes the prior art of Chang using training sets for gene expression analysis in 2005, prior to the effective filing date of the instant application (FF 2).

Appellants contend: "It is indisputable that every step in this claim is *not* 'a familiar part of the conscious process that doctors can and do perform in their heads.' For at least this reason, the *Smartgene* decision is entitled to no weight in deciding the present case" (Reply Br. 4).

We find this argument unpersuasive. The claims at issue in *SmartGene* relied upon "expert rules for 'evaluating and selecting' from a stored 'plurality of different therapeutic treatment regimens."' *SmartGene*, 555 F. App'x. at 951–952, claim 1). The "expert rules" in *SmartGene* are analogous to the "correlating" step using "random training datasets" to

identify top genes in claim 6. In neither *SmartGene* nor the instant claims is there any evidence of record that specific rules or factors were required, that the steps represented something "significantly more" than the prior art, or that Appellants invented new computer software or analysis techniques not known in the prior art for the analysis (*see, e.g.*, FF 1–7).

We have considered, but find unpersuasive, Appellants' reference to the Federal Circuit decisions *SiRF Tech., Inc. v. Int'l Trade Comm'n*, 601 F.3d 1319 (Fed. Cir. 2010) and *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366 (Fed. Cir. 2011), *Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859 (Fed. Cir. 2010) (*see* Reply Br. 4–5), all decided prior to the binding precedent of the Supreme Court decisions of *Mayo* and *Alice*. We are constrained by *Mayo* and *Alice*, and for the reasons given, find that claim 6 does not satisfy the two-part test for patentable subject matter presented in *Mayo* and *Alice*.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that claim 6 is directed to non-statutory subject matter.

SUMMARY

We affirm the rejection of claim 6 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Claims 7–17 fall with claim 6.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED